Prescription-, Illicit-, and Self-Harm Opioid Overdose Cases Treated in Hospital

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ABSTRACT. Objective: Research suggests unintentional overdose on prescription drugs and intentional self-harm cases differ fundamentally from unintentional illicit drug overdoses, but there are few data on opioid overdose per se. **Method:** We analyzed consecutive opioid overdose patients age 13 and over (N = 435) treated by a toxicology consult service to compare three poisoning groups: unintentional illicit drug (illicit, n = 128), unintentional prescription drug (prescription, n = 217), and intentional self-harm (self-harm, n = 90). The groups were compared on key characteristics of the poisoning events (severity, co-ingestion of non-opioid) and the hospital-based treatments required to manage the poisonings (use of antidote, provision of pharmacological support). Logistic regressions yielded incident rate ratios (IRRs) and 95% confidence intervals (CI) adjusted for age and sex. **Results:** Compared to the illicit group, the prescription group was more likely to co-ingest a non-opioid drug (IRR [95% CI] = 1.594 [1.077, 2.358], p = .020. Compared to illicit cases, self-harm cases were more likely to co-ingest a non-opioid drug (IRR = 3.181 [1.620, 6.245], p = .001) and had a lower poisoning severity score (IRR = 0.750 [0.564, 0.997], p = .048). There were no statistically significant differences between the self-harm and prescription groups. **Conclusions:** The similarities between the self-harm and prescription poisoning groups suggest that they may benefit from common interventions including appropriate restriction on prescription of opioids and other medications that may be misused (e.g., sedative-hypnotic/muscle relaxants). The characteristics of the illicit poisoning group (use of heroin; more severe overdose events) suggest the need for initiation of intensive substance use treatment interventions during hospitalization. (*J. Stud. Alcohol Drugs, 79,* 893–898, 2018)

THE RATE OF POISONING DEATHS in the United States has risen dramatically in the past two decades (Hedegaard et al., 2017), and the recent drop in the nation's average life expectancy has been attributed to the increase in poisoning deaths (Kochanek et al., 2017). The increase in overdose deaths has been driven by opioid ingestions that account for nearly two thirds of all poisoning deaths (Rudd et al., 2016). Although opioid-related mortality statistics are daunting, most opioid poisoning cases are nonfatal, and dramatic increases in hospital inpatient and emergency department visits for nonlethal opioid poisoning events have also been observed (Centers for Disease Control and Prevention, 2018; Weiss et al., 2016; Yokell et al., 2014). These hospital patients may be presumed to be at high risk for overdose recurrence and death (Hser et al., 2017), particularly those who present to treatment repeatedly (Brady et al., 2015). As a result, it is essential to engage and intervene with opioid overdose patients during hospital presentation to prevent recurrence. However, the design and testing of such interventions is at an early stage, and amassing data on these cases is essential to guide treatment efforts.

Complicating the design of preventive interventions, opioid overdose cases are heterogeneous including whether the opioid(s) are illicit (e.g., heroin) or prescription (e.g., oxycodone), and whether the poisoning is unintended or intentional (i.e., suicide) (Buykx et al., 2010; Compton et al., 2016; Hedegaard et al. 2017; Rockett & Caine, 2015; Rudd et al., 2016). The importance of these distinctions is underscored by research showing that users of prescription versus illicit opioids, most commonly heroin, differ in many key respects (e.g., heroin users more likely to be male, greater drug use severity, higher mortality risk) and that nearly all heroin users have used prescription opioids whereas a small percentage of prescription opioid users have used heroin (Compton et al., 2016). Accordingly, prescription opioid users and illicit opioid users are overlapping yet distinct populations that are likely to require tailored prevention strategies (Compton et al., 2016). Moreover, a study in Australia showed that, compared to illicit drug overdose patients, intentional self-poisoning patients (i.e., suicide attempters) and unintended prescription drug overdose cases differed in key respects including having lower acute poisoning severity and higher likelihood of hospitalization (Buykx et al., 2010). In sum, the data suggest that illicit drug overdose cases stand out in important ways from overdose cases of intentional self-harm and prescription drugs, with implications for tailoring preventive interventions.

The purpose of the current study was to examine the heterogeneity in opioid overdose cases presenting to the hospital by comparing three groups of patients including

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unintentional poisoning cases using illicit drugs (illicit) and prescription drugs (prescription), along with intentional self-poisoning cases (self-harm). We compared these groups on poisoning characteristics (e.g., severity) and acute treatment experiences (e.g., provision of antidote) based on the hypothesis that illicit cases would differ from the other groups (prescription, self-harm) on these variables (Buykx et al., 2010; Compton et al., 2016). We also compared the prescription- and self-harm cases.

Method

Procedure

Structured information on all patients treated in the hospital and seen by a university medical center–based toxicology consultation team between November 17, 2010, and December 8, 2016, were entered by trained members of the team into a de-identified, central database maintained by the Toxicology Investigators Consortium Registry, ToxIC Registry (Rhyee et al., 2015). The approximate 6-year study period coincides with the onset of data collection using the study instruments and the last date for institutional review board–approved analysis. Data were entered as standard codes developed for the ToxIC Registry based on clinical judgment using available information including patient interview (primary source), observations of family members and emergency medical technicians, and laboratory findings including toxicology test results. Most data were abstracted from the electronic medical record including, but not limited to, review of admission notes, the discharge summary, and consultation notes provided by the toxicology consult service.

The current analyses were a subset of opioid overdose cases treated by the local team that met the following inclusion criteria: (a) acute poisoning event, (b) exposure to one or more opioids in the event, and (c) patient age 13 and older. We excluded from analyses patients using their own prescriptions in a manner or dose as prescribed and who did not appear to meet criteria for prescription drug misuse (National Institute on Drug Abuse, 2018). Codes for intention of poisoning (intentional self-harm; unintentional poisoning events attributable to misuse, for example to "get high" or to use in a way outside of prescription) and source of opioids (illicit, prescription) were used to create three study groups: intentional self-harm (self-harm); unintentional, illicit drug poisoning (illicit); and unintentional, prescription drug poisoning (prescription). Patients with self-harm, regardless of the source of the opioid, were combined into a single self-harm group, necessitated by the small number of cases (n = 4) of intentional self-harm using illicit opioids, with the remaining intentional self-harm patients using prescription opioids. Unintentional poisoning cases using both illicit opioids (e.g., heroin) and prescription drugs (e.g., oxycodone) were coded as illicit. Patients using a prescription drug obtained from a family member, friend, or on the street (but not their own prescription) were coded as illicit. The study was conducted with the approval of the local university's human subjects' review committee.

Independent variables

Drug categories including opioid and non-opioid drug (e.g., benzodiazepine) were based on those established for the ToxIC Registry (Rhyee et al., 2015). We used Poisoning Severity Score (PSS) as the primary measure of medical severity of overdoses (Persson et al., 1998). PSS is a validated measure of poisoning severity with values of *none* (0), *minor* (1), *moderate* (2), *severe* (3), *fatal* (4). For the current analysis, the severe (3) and fatal (4) groups were combined into one category because of the low number of overdose fatalities (n = 2), yielding a poisoning severity measure with range of 0–3. The PSS predicts morbidity and mortality in patients presenting to the hospital (Peter et al., 2013; Thanacoody et al., 2016) and it is correlated with other validated measures of acute medical morbidity (Akdur et al., 2010; Churi et al., 2012; Peter et al., 2013), which are both indicators of the validity of PSS. We also compared the study groups on whether opioids were co-ingested with another class of drug (e.g., benzodiazepine) in the poisoning event, and if the patient required hospital-based pharmacological interventions to manage the poisoning including provision of an antidote (treatment provided, not provided) or other type of pharmacological support (treatment provided, not provided).

Analyses

Logistic regression models (Agresti, 2002; Hosmer & Lemeshow, 2000) adjusted for age and sex were used to compare the three study groups (illicit, prescription, self-harm) on characteristics of poisoning (i.e., co-ingestion, poisoning severity) and hospital-based medication treatments for poisoning (i.e., antidote, pharmacologic support). Models report incident rate ratios (IRRs), rather than odds ratios, as the latter can lead to overestimates when the incidence of the dependent variable exceeds 10% (Zhang & Yu, 2018). Separate models were run to examine each characteristic adjusted for sex and age, which was categorized as 13–18 years, and 19 and older. Statistical significance was based on $p < .05$. Analyses were conducted using Stata 15 (StataCorp LP, College Station, TX).

Results

There were 435 cases meeting study eligibility including 41 (9%) patients age 13–18 and 196 (45%) female. Unintentional prescription opioid overdose cases were most common

Table 1. Comparisons of demographic, clinical, and service provision characteristics of groups of opioid poisoning cases ($N = 435$)

Independent variable	Illicit ($n = 128$) n (%) or M (SD)	Prescription ($n = 217$) n (%) or M (SD)	Self-harm ($n = 90$) n (%) or M (SD)	Prescription vs. illicit (ref.) IRR [95% CI]	p	Self-harm vs. illicit (ref.) IRR [95% CI]	p	Self-harm vs. prescription (ref.) IRR [95% CI]	p
Co-ingestion of non-opioid drug (ref.: no co-ingestion)	65 (51%)	167 (77%)	78 (87%)	1.594 [1.077, 2.358]	.020	3.181 [1.620, 6.245]	.001	1.559 [0.795, 3.057]	.196
Poisoning Severity Score	2.43 (0.84)	1.98 (0.95)	1.96 (0.88)	0.816 [0.649, 1.025]	.081	0.750 [0.564, 0.997]	.048	0.990 [0.752, 1.303]	.941
Antidote administered (ref.: not provided)	90 (70%)	123 (57%)	57 (63%)	0.823 [0.582, 1.164]	.270	0.922 [0.545, 1.562]	.764	1.300 [0.794, 2.129]	.297
Pharmacological support provided (ref.: not provided)	36 (28%)	51 (24%)	29 (32%)	0.932 [0.624, 1.392]	.732	1.144 [0.662, 1.976]	.629	1.430 [0.847, 2.415]	.181

Notes: Column percentages shown. Subjects with missing Poisoning Severity Score data ($n = 112$) were excluded from comparisons of poisoning severity. PSS scores had range or 0–3. Illicit = unintentional illicit drug poisoning; prescription = unintentional prescription drug poisoning; self-harm = intentional self-harm; ref. = reference; IRR = incident rate ratio, with adjustment for age and sex; CI = confidence interval.

(prescription, $n = 217$, 50%), followed by illicit drug use (illicit, $n = 128$, 29%) and intentional self-harm (self-harm, $n = 90$, 21%). The three study groups did not differ on sex or age categories at a statistically significant level, with the exception that a greater proportion of females were in the self-harm group (52%) than the illicit group (34%) ($p = .029$). The specific opioid agents ingested in prescription and self-harm cases, respectively, were similar. The most common opioid agents ingested in prescription and self-harm cases included oxycodone (28% of prescription cases, 28% of self-harm cases), hydrocodone (19%, 20%), tramadol (13%, 17%), and methadone (17%, 6%). In the illicit group, heroin ingestion predominated (85%), and other agents included oxycodone (9%), buprenorphine (5%), morphine (3%), methadone (2%), and hydrocodone (2%).

PSS data were available in 313 (72%) cases and were as follows: PSS = 0 ($n = 23$), PSS = 1 ($n = 48$), PSS = 2 ($n = 115$), PSS = 3 ($n = 127$), PSS = 4 ($n = 2$). The cases with missing PSS data ($n = 122$, 28%) were excluded from analyses of poisoning severity. Co-ingestions of non-opioid classes of drugs occurred in about half of illicit cases (51%) and in the majority of prescription (77%) and self-harm (87%) cases. Similar drugs were co-ingested in prescription and self-harm cases, most commonly sedative-hypnotic/muscle relaxants (47% of prescription cases, 41% of self-harm cases), non-opioid analgesics (29%, 36%), and antidepressants (13%, 24%). In illicit cases, the most commonly co-ingested categories of drugs were sympathomimetics, most commonly cocaine (27%), and sedative-hypnotic/muscle relaxants (25%). Alcohol co-ingestion was as follows: prescription cases (7%), self-harm (18%), illicit (13%).

Results of analyses comparing the prescription and self-harm groups, respectively, to the illicit group are shown in Table 1. Compared to illicit cases, prescription cases more likely to co-ingest a non-opioid drug (IRR [95% CI] = 1.594 [1.077, 2.358], $p = .020$) and showed a nonsignificant trend ($p < .10$) for a lower poisoning severity score (IRR = 0.816 [0.649, 1.025], $p = .081$]. Compared to the illicit group, the self-harm group was more likely to co-ingest a non-opioid drug (IRR = 3.181 [1.620, 6.245], $p = .001$) and had a lower poisoning severity score (IRR = 0.750 [0.564, 0.997], $p = .048$). These groups did not differ on the likelihood of use of receipt of a pharmacological intervention (i.e., provision of antidote, pharmacological support) to manage the poisoning at the hospital bedside. There were no statistically significant differences between the self-harm and prescription groups.

Discussion

We analyzed 435 consecutive opioid poisoning patients treated in the hospital and seen by an academic medical center toxicology consult service. Results suggest that unintentional overdose on prescription drugs (prescription) and intentional self-harm (self-harm) cases have many similarities including similar age and sex characteristics; high rates of co-ingestion of sedative-hypnotic/muscle relaxants, non-opioid analgesics, and antidepressants; and similar poisoning severity and likelihood of receiving hospital-based pharmaceutical interventions to manage poisoning. These results are generally consistent with Buykx and colleagues' (2010) report, which described the similarity of overdose presentations for self-harm and prescription cases, and suggests the pattern applies to opioid-related poisoning hospitalizations in the United States.

The similarities of prescription and self-harm opioid poisoning cases suggest the value of common prevention strategies including the use of judicious prescription of opioids for chronic pain or related conditions (Califf et al., 2016; Dowell et al., 2016). Yet, following an opioid-related hospital stay, only a small portion of individuals receive appropriate medication-assisted treatment (Nager et al., 2016), and patients with opioid-related hospital stays as well as those receiving care for chronic pain are commonly given ill-advised prescriptions, including opioids in combination with benzodiazepines, that have high potential for adverse consequences including overdose death (Gomes et al., 2011;

Nager et al., 2016; Park et al., 2015). Prioritization of safer, efficacious alternatives such as mindfulness-based stress reduction or cognitive-behavioral treatment are needed (Ehde et al., 2014; Maglione et al., 2016). Although prescription and self-harm patients have many similarities, these patient groups may also benefit from treatments that are unique to their presenting problems, for example linking self-harm patients with behavioral interventions explicitly designed to reduce risk of repetition of suicidal behavior (Brown et al., 2005; Gysin-Maillart et al., 2016).

The frequent co-ingestion of opioids and sedative-hypnotic/muscle relaxants in the prescription- (47%) and self-harm groups (41%) bears mention because sedative-hypnotic/muscle relaxants are associated with increased risk of overdose when taken with opioids even at low doses (Abrahamsson et al., 2017; Garg et al., 2017). Poisoning patients who co-ingest opioids and sedative-hypnotic/muscle relaxants, both of which produce euphoric effects and are prone to misuse, frequently have an ongoing pattern of prescription drug misuse. To address this co-ingestion, statewide Prescription Monitoring Programs (PMPs) could be used to assess these and other poisoning patients' histories and to collaborate with outpatient prescribers during hospitalization. Research indicates that PMPs are associated with a variety of beneficial effects related to the opioid epidemic and harms associated with opioid use (Ali et al., 2017). Unfortunately, not all states have robust PMPs or associated provider mandates, and certainly not all emergency department or hospital providers review the PMP when caring for an overdose patient. Indeed, a recent study reported that it was common for patients to continue receiving the same prescriptions after overdose resulting in hospitalization (Larochelle et al., 2016). One potential remedy is for prescribers to make maximum use of PMPs as they currently exist. Another is to expand the nature of inclusion in a PMP such that a broader range of medications involved in poisoning cases may be included, with the potential to reduce opioid-related harms (Patrick et al., 2016). One gap is that not all sedative-hypnotics/muscle relaxants are controlled and displayed in the PMP. For example, gabapentin, a non-controlled sedating medication in this class, has been increasingly associated with misuse among opioid users (Buttram et al., 2017; Lyndon et al., 2017). In response, some states have started classifying gabapentin differently and begun to include it in their state PMP (e.g., Kentucky and Ohio). Underscoring the relevance of this topic, among current prescription and self-harm patients who co-ingested opioids and sedative-hypnotics/muscle relaxants, 17% and 11%, respectively, had used gabapentin.

Results indicate that illicit drug users (illicit) differ from the other study groups, including being less likely to co-ingest a non-opioid drug and to experience more severe poisoning. The data further show that illicit drug use patients were most likely to overdose on heroin per se. Heroin use marks a severe opioid use population at risk for a range of negative consequences including early mortality, job loss, incarceration, and infectious disease (Fleischauer et al., 2017; Richardson et al., 2010). Heroin users are generally in need of aggressive substance use intervention, for example medication-assisted treatment, which may be initiated during hospitalization (Englander et al., 2017; Liebschutz et al., 2014). Along with inpatient initiation of medication-assisted treatment (e.g., buprenorphine or methadone), particularly for use with heroin users with opioid use disorder, other interventions can be effective in this setting including discussing a referral for treatment and providing information or facilitating contact with a treatment program (Pollini et al., 2006). In addition, naloxone distribution in the emergency department setting may also hold utility for these patients. Generally, naloxone access is associated with reduced opioid overdose mortality (e.g., Heavey et al., 2018; McClellan et al. 2018); however, distribution programs are primarily associated with needle exchanges and other outpatient services (Clark et al., 2014). These findings suggest that initiating naloxone distribution before discharge from the emergency department is a potential opportunity to reduce opioid overdose mortality.

Although the analyses indicated that self-harm and prescription cases showed lower poisoning severity than illicit cases, a high percentage in each group (71%, 74%, 88%) showed at least moderate poisoning severity, defined as PSS score of 2 or greater. These results highlight the seriousness of opioid-related poisonings, regardless of their etiology. Accordingly, although it is not a panacea, a naloxone kit (an opioid antagonist to reverse acute opioid effects in the event of overdose) and education in its use should be routinely offered to all opioid overdose patients (illicit, prescription, self-harm) who come to acute medical attention (Dwyer et al., 2013; Strang et al., 2014).

There were limitations of the study. It was a secondary analysis of cross-sectional data. We did not have reliability data on PSS, for example by comparing two independent raters. The comprehensiveness of toxicological analysis varied among patients. Heroin users may have used additional agents (e.g., fentanyl, fentanyl analogues) not detected in toxicological analyses that were cut with heroin or even fully substituted, a phenomenon that is increasingly common (Ciccarone, 2017). We had the benefit of direct interview data from patients to inform judgments about intentionality (i.e., suicidal, unintentional). As a result, the validity of our categorizations of cases is presumed to be higher than can be achieved in fatal cases examined postmortem that rely on secondary sources of information (Rockett et al., 2018). Nonetheless, some misclassification is inevitable because not all patients are revealing about their suicidal intent and select cases have characteristics that make categorization challenging (e.g., an illicit drug user who has become hopeless about recovery and knew the bolus of drugs injected could be fatal, but denies suicidal intent). The research took

place at a large, urban, university-based medical center in the northeastern United States, with unclear generalizability to other settings. There were also several strengths of the study including systematic comparisons of major types of opioid-related poisonings, with significant public health and clinical implications; descriptive data across a wide range of opioid agents used and categories of co-ingested drugs; and data on poisoning severity that is rarely reported in studies of suicidal behavior. Results support the idea that the source of opioid (prescribed, illicit) and nature of the ingestion (intentional, unintentional), in combination, inform the identification of subgroups of opioid overdose patients with differing characteristics and treatment needs.

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